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Effects of Chronic Amitriptyline and Desipramine on Food Intake and Body Weight in Rats

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NOBREGA, J. N. AND D. V. COSCINA. *Effects of chronic amitriptyline and desipramine on food intake and body weight in rats.* PHARMACOL BIOCHEM BEHAV **27**(1) 105–112, 1987.—Long-term treatment with tricyclic antidepressant drugs (TCAs) can induce excessive body weight gain in a significant proportion of patients. Such weight gains, which appear to be largely independent of clinical improvement, are in many cases severe enough to interfere with continuation of treatment. In efforts to model this effect in experimental animals, seven experiments were performed in which two commonly used TCAs, amitriptyline and desipramine, were administered chronically to rats. Despite manipulations of drug dosages (2.5 mg–17 mg/kg), route of administration (intraperitoneal, subcutaneous, oral; daily injections vs. continuous release from osmotic pumps), diet composition and palatability (regular Purina Chow pellets or powder with or without added high fat and high carbohydrate sources; high vs. low protein diets) and animal sex and housing conditions (single vs. group housing), chronic TCA treatment was never observed to increase daily food intake or rates of body weight gain. Desipramine treatment invariably caused decreased food intake and weight loss. Amitriptyline treatment either caused no change in food intake and body weight or slightly reduced levels in comparison to vehicle-treated controls. However, both amitriptyline- and desipramine-treated rats showed a potentiation of acute caloric intake after a single systemic injection of the glucoprivic agent 2-deoxy-D-glucose. These results are considered against the background of human clinical observations. Possible reasons for the differences between human and animal data are discussed.

Amitriptyline Appetite Body weight Chronic tricyclic antidepressant Desipramine
2- Deoxy-D-glucose Food intake Rat

CHRONIC treatment with tricyclic antidepressants (TCAs) in patients often causes considerable increases in body weight (b.wt.) and significantly interferes with continuation of therapy [4,19]. Although this particular side effect was recognized early on [3,18], it received only a modest amount of systematic attention until recently. Since appetite changes and weight loss are common symptoms of affective disorders [30], it is often thought that increases in appetite and/or b.wt. simply reflect clinical improvement. It has even been suggested [20] that increases in b.wt. be viewed as a marker for the beginning of clinical recovery. It is now clear, however, that the b.wt. gain associated with chronic TCAs is not necessarily a reflection of their therapeutic effects. In fact, such b.wt. changes are often reported to be largely independent of clinical improvement [18, 21, 29, 31]. Also noteworthy is the fact that while both tricyclics and non-tricyclics can be equally effective in treating depressive illness, the literature indicates that b.wt. gain is consistently associated with tricyclics but not with non-tricyclic antidepressants. Examples include controlled comparisons involving TCAs such as amitriptyline, imipramine or doxepin on the one hand and non-tricyclics such as zimelidine, trazodone and bupropion on the other [1, 11, 12, 16, 19, 21, 29]. An early suggestion that TCA-induced weight gain might be due to hyperinsulinemia [39] has not been confirmed in a controlled investigation by Paykel [31]. The latter investigators found no difference in fasting levels of plasma glucose or insulin from patients displaying excessive weight gain after 9 months of treatment with amitriptyline when compared to placebo-treated patients.

If TCA-induced changes in appetite and/or b.wt. gain are indeed independent of their psychiatric effects, one would expect these drugs to produce similar effects on experimental animals. Such an expectation is reinforced by the fact that chronic TCA treatment is also known to affect the functional status of central neurochemical systems that have been implicated in the control of appetite and feeding behaviour (see [22] for review). Examples include the well-documented changes in synaptic availability and/or receptor sensitivity in noradrenergic and/or serotonergic systems as a result of prolonged TCA treatment (see [23] for review). Surprisingly, however, the literature contains few systematic

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investigations of the effects of chronic TCA treatment on food intake and body weight regulation in experimental animals (see [14] for recent review). Here we report the results of a series of experiments on the effects of chronic TCAs on food intake and body weight in rats. The studies focussed on amitriptyline (AMI), the TCA which has been most often implicated in excessive weight gain in clinical populations. A number of variables, including drug dosages, routes of administration, and diet composition, were manipulated in attempts to define the conditions under which chronic AMI treatment might lead to exaggerated food intake and/or weight gain. As described below, under no conditions did we observe increased intake or weight gain as a result of chronic TCA treatment.

GENERAL METHOD

Subjects

A total of 129 Wistar rats (Woodlyn Farms, Guelph, Ontario) were used in 7 separate experiments. Except for Experiment 5, female rats weighing 200–225 g at the beginning of experiments were used. Unless otherwise stated, animals were individually housed in hanging wire-mesh cages in temperature-controlled (21±1°C) rooms. Lights were on between 0800 and 2000 hr daily. Before any drug treatments were initiated, animals were allowed at least one week adaptation to the laboratory. An additional 10 days of adaptation were allowed when diets other than regular Purina Chow were used.

Measurements

In all experiments, body weight, food intake and water intake were measured daily. Powdered diets were given in Wahmann metal cups fastened to the bottom of the cages. Drug injections and measurements were always done between 0830 and 1130 hr by the same investigator.

Drugs

Amitriptyline and desipramine (DMI) were gifts from Merck Sharp and Dohme of Canada and Ciba-Geigy of Canada, respectively. In experiments involving daily drug administration, drug solutions were prepared fresh each day in 0.9% saline and injected in concentrations of 10 mg/ml.

Plasma Assays and Statistical Analyses

Except where noted, animals were decapitated at the end of the experiments and trunk blood was collected, centrifuged and frozen. Determinations of plasma AMI and DMI were done by gas chromatography on a Varian 3700 equipped with a nitrogen-phosphorus detector using the method of Cooper *et al.* [9] as modified by Cooke *et al.* [8]. Clomipramine and desmethylclomipramine were used as internal standards for AMI and DMI, respectively. Statistical analyses of behavioural data were performed by repeated measures Analyses of Variance and/or *t*-tests for correlated or uncorrelated samples.

EXPERIMENT 1

Female rats were given ad lib access to isocaloric high- and low-protein diets containing 60% and 10% casein by weight, respectively. Cornstarch, which is a carbohydrate isocaloric to casein, was substituted for casein to produce the low-protein diet. A description of the other diet ingredients has been reported previously [2]. After 10 days of adaptation to the powdered diets, animals received daily intraperitoneal (IP) injections of either amitriptyline (AMI, 10 mg/kg), desipramine (DMI, 10 mg/kg) or equivalent volumes of saline vehicle (1 ml/kg) for 28 days. On the 25th day of drug administration, general locomotor activity was assessed in all rats in a square 0.49 m^2 open-field. Ambulation was automatically recorded by infrared photobeams placed at 20 cm intervals along the walls. The 15-min open-field test preceded the daily injection. Twenty-four hr after the last injection 1 ml blood samples were collected from all animals by intracardiac puncture under light ether anesthesia. Plasma was separated and frozen at −70°C for subsequent determination of drug concentrations.

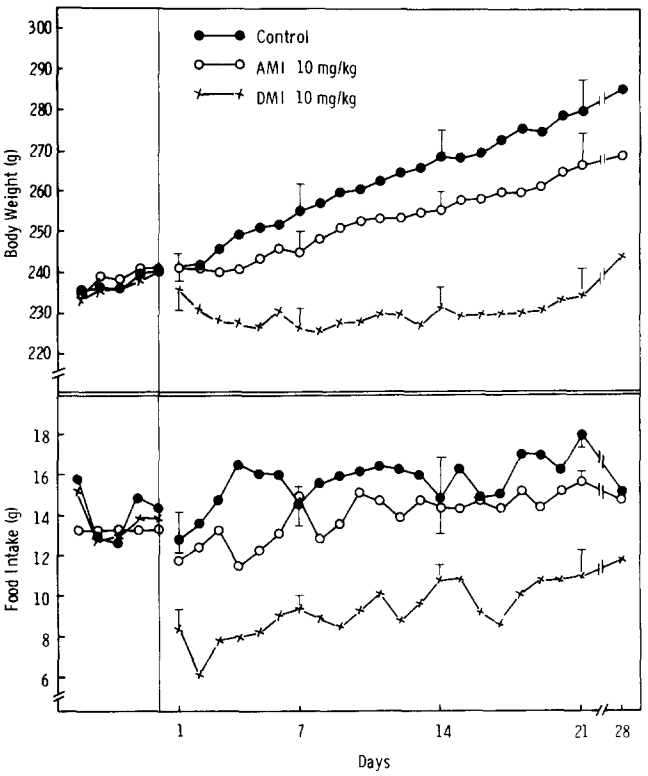

FIG. 1. Body weight and total food intake data for 28 days of amitriptyline (AMI), desipramine (DMI) or vehicle in Experiment 1. The vertical line separates baseline from injection days. Each point is the mean of 6 animals. Error bars represent standard errors of the mean.

Results

Body weight and total food intake data are presented in Fig. 1. As can be seen, a significant drop in total food intake and b.wt. gain occurred in the DMI-treated group as soon as drug treatment was initiated ($p<0.01$). There was also a tendency for AMI-treated rats to display lower than control levels of both FI and b.wt. gain starting approximately one week after drug treatment began, but these effects were not statistically significant ($p>0.05$).

Total protein consumption declined in the DMI group, (−34% compared to pre-drug baseline; −42% compared to

post-injection mean control level, $ps<0.002$), but it remained a constant fraction of the total food consumed (34% pre-drug vs. 31% post-drug). On the 19th day of drug administration food and fluid intake were also measured 2 hr after the injections to determine if short-term changes might occur in macronutrient selection. There were no differences in the total amount consumed by the three groups (DMI=1.68 g±1.81; AMI=1.95 g±1.12; Controls=1.77 g±0.78) or in the percentage of those amounts consumed as protein (DMI=35±21%; AMI=33±15%; Controls=44±15%).

Results of open-field testing on the 25th day of drug administration revealed lower activity levels for DMI rats compared to vehicle-treated controls (−17%, $p<0.05$). AMI-treated rats had a non-significant 12% decrease in open-field line crossings compared to vehicle-treated controls (DMI=842±97; AMI=892±203; Controls=1017±119).

Twenty-four hr after the last injection DMI treated rats had a mean plasma level of 107 ng/ml (range: 60–185 ng/ml). Somewhat unexpectedly, none of the 6 AMI-treated rats had measurable plasma concentrations of the drug at that time.

EXPERIMENT 2

After the first few days of injections in Experiment 1, DMI-injected rats began to show signs of peritoneal discomfort following each daily injection. Therefore in a second experiment we attempted to avoid potential local irritative effects of daily injections by mixing the drugs in the animals' drinking water. It was also hoped that this route of administration might result in higher plasma concentrations of AMI. Concentrations were 0.1 mg/ml for DMI and 0.2 mg/ml for AMI. The same diets as used in Experiment 1 were employed.

Results

After 21 days of drug treatments, mean daily drug intake was 6.5±1 and 13.2±1 mg/kg for DMI and AMI groups, respectively. Body weight and total FI data (Fig. 2) followed a pattern similar to that seen in Experiment 1, except that DMI rats showed a gradual recovery in FI but not in b.wt. Daily fluid intake (data not shown) was equal to that observed in Experiment 1 for all three groups, paralleling daily food intake at every point. Protein intake declined in both drug groups: −33% ($p<0.02$) and −20% ($p<0.05$), compared to pre-drug baseline levels for DMI and AMI groups, respectively. Mean daily protein intake for DMI and AMI groups was −33% ($p<0.02$) and −15% (NS) of control values during the 21 days of drug treatment. As in Experiment 1, there were no changes in the percentage of daily calories consumed as protein for any of the treatment groups.

On the 17th treatment day all rats were tested in the open field as described in Experiment 1. There were no differences among the 3 groups in total line crossings (DMI=941±159; AMI=1023±127; Controls=953±169).

Mean plasma level of DMI 24 hr after discontinuation of treatment was 94.6 ng/ml (range: 41–128 ng/ml). As in Experiment 1, only negligible amounts of AMI were found in plasma at that time.

EXPERIMENT 3

This experiment addressed the possibility that TCA treatment might induce chronic changes in general motoric activity, which might in turn affect FI and/or b.wt. gain. Animals were individually housed in Wahmann metal cages (15.2×25.4×13 cm each) with continuous access to attached running wheels. The total number of wheel revolutions was recorded daily for each animal. Purina lab chow in powdered form was used. After a two-week adaptation period to the cages and the diet, daily IP injections of DMI (10 mg/kg), AMI (10 mg/kg) or vehicle were initiated. Injections were maintained for 5 weeks, after which animals were sacrificed and trunk blood was collected for plasma assays.

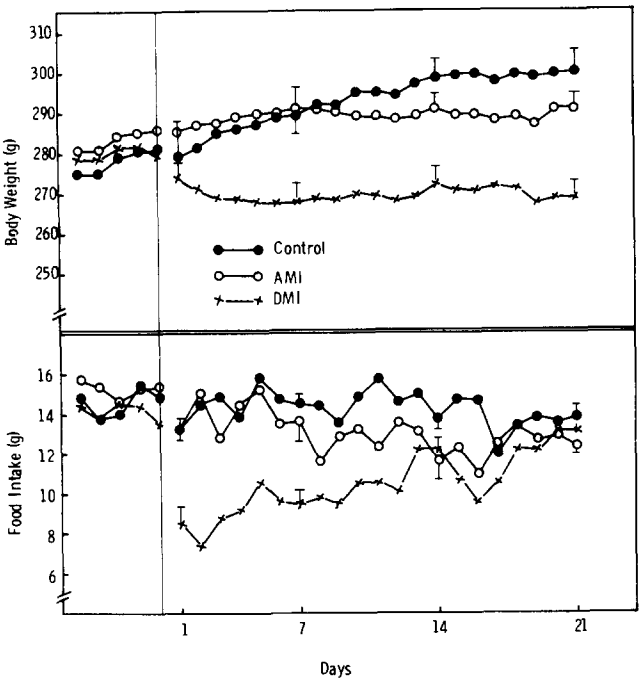

FIG. 2. Body weight and total food intake data for 21 days of oral amitriptyline (AMI), desipramine (DMI) or vehicle in Experiment 2. See text for description of average daily doses. The vertical line separates baseline from injection days. Each point is the mean of 6 animals. Error bars represent standard errors of the mean.

Results

As shown in Fig. 3, no significant differences were observed among groups in rates of b.wt. gain or FI during 21 days of drug treatment. FI data for all groups were more variable and rates of b.wt. gain were lower for all groups than in the previous experiments. DMI-treated rats again showed an initial drop in FI followed by a gradual recovery. During the injection period, both drug-treated groups showed lower mean levels of running than controls (−35% and −28% for DMI and AMI groups, respectively; both $ps<0.02$). Mean plasma level of DMI 24 hr after the last injection was 318 ng/ml (range: 180–442 ng/ml). Plasma AMI levels were again negligible.

EXPERIMENT 4

Continuous monitoring of motor activity in Experiment 3 revealed that 10 mg/kg/day of DMI and AMI resulted in lower than control levels of running activity in both groups. In an effort to reduce motoric effects, dosages of DMI and

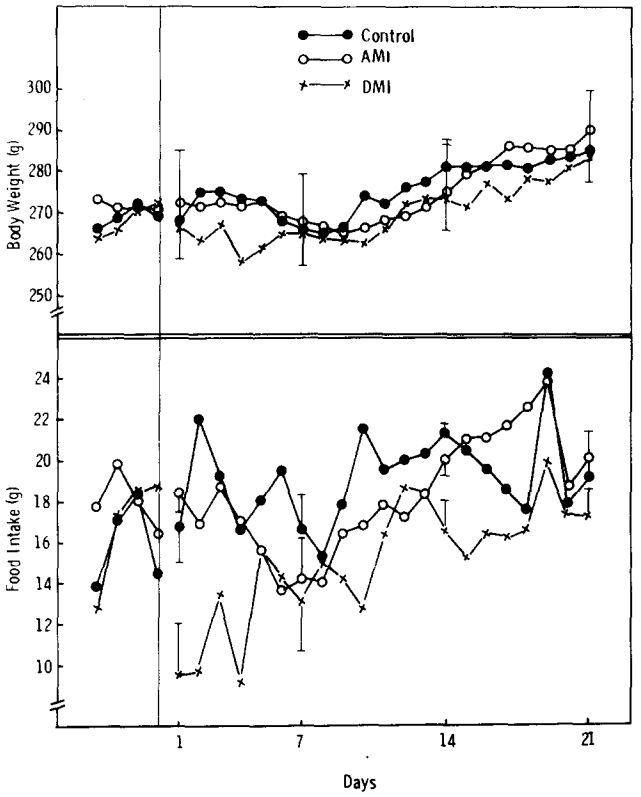

FIG. 3. Body weight and food intake data for 21 days of amitriptyline (AMI, 10 mg/kg, IP), desipramine (DMI, 10 mg/kg, IP) or vehicle in Experiment 3. The vertical line separates baseline from drug administration days. Each point is the mean of 6 animals. Error bars represent standard errors of the mean.

AMI were reduced to 2.5 mg/kg in the next experiment. In addition, since patients receiving long-term TCA treatment often report a craving for sweet-tasting foods [3, 18, 31], rats in this experiment were given access to a 33% sucrose solution in addition to powdered Purina chow and water. Measurements of food, water and sucrose intake were made 2 hr and 24 hr after the daily IP injections. On the 33rd treatment day rats were given a glucoprivic challenge by injecting 750 mg/kg of 2-deoxy-D-glucose (2-DG, Sigma, St. Louis) IP. Food, water and sucrose intake were monitored hourly for 6 hr.

Results

Total food intake, sucrose intake and b.wt. gain data are shown in Figs. 4, 5 and 6. Introduction of daily antidepressant treatments produced effects similar to those seen in the preceding experiments. The 2.5 mg/kg DMI dose did not produce an initial drop in b.wt., but the animals still gained weight at a lower pace than controls or AMI-treated rats (Fig. 4). DMI suppressed daily sucrose and total caloric intake, while AMI-treated animals were not significantly different from vehicle-treated rats (Figs. 5 and 6). There were no significant pre- vs. post-drug differences in acute (2 hr) sucrose intake, nor were there any pre- vs. post-drug changes in the percentage of daily calories ingested as sucrose in any of the three groups (Figs. 5 and 6).

Intraperitoneal 2-DG induced the expected acute increases in food, sucrose and water intakes. Both TCA-treated groups tended to ingest more powdered Chow, water and sucrose than controls, although the differences did not reach statistical significance on any of these measures (Table 1). However, when total caloric intake over 6 hr was computed, both AMI and DMI rats were found to have consumed significantly more than controls (+32% and +42%, respectively; $ps<0.05$) (Table 1).

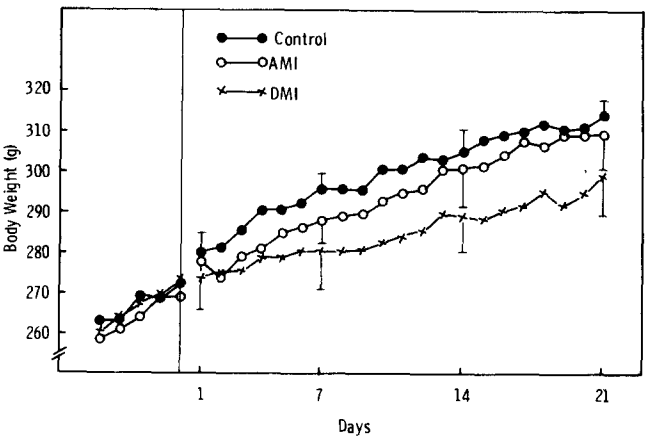

FIG. 4. Body weight data for 21 days of amitriptyline (AMI, 2.5 mg/kg IP, n=8), desipramine (DMI, 2.5 mg/kg IP, n=6) or vehicle (n=5) in Experiment 4. The vertical line separates baseline from drug administration days. Error bars represent standard errors of the mean.

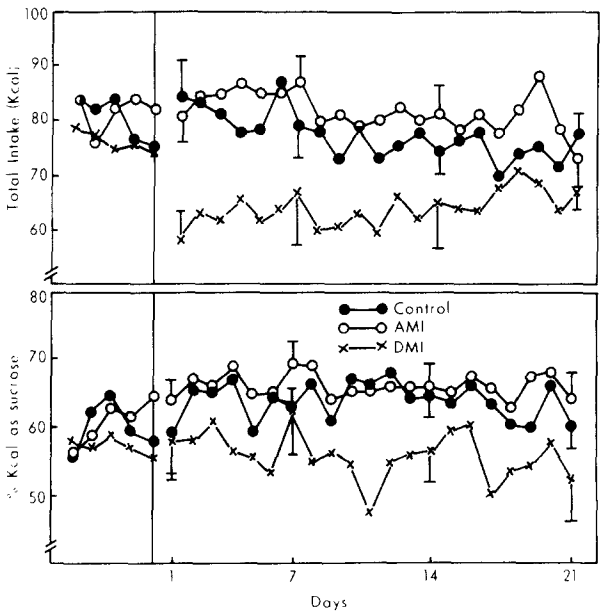

FIG. 5. Total caloric intake and percent of total calories ingested as sucrose for amitriptyline- (AMI, 2.5 mg/kg IP, n=8), desipramine- (DMI, 2.5 mg/kg IP, n=6) or vehicle- (n=5) treated rats in Experiment 4. The vertical line separates baseline from drug administration days. Error bars represent standard errors of the mean.

TABLE 1

EFFECTS OF 2-DEOXY-D-GLUCOSE ON FOOD, WATER AND SUCROSE INTAKE IN EXPERIMENT 4†

	N	Food (g)	Water (ml)	Sucrose (ml)	Total kcal
AMI	8	1.50 ± 0.35	5.12 ± 1.33	10.87 ± 1.46	18.40 ± 1.20*
DMI	6	1.65 ± 0.50	7.00 ± 0.89	11.50 ± 1.98	19.74 ± 1.64*
Controls	5	0.80 ± 0.27	3.80 ± 1.16	9.20 ± 0.86	13.92 ± 1.30

*$p<0.05$, t-test vs. controls.
†Numbers are means ± sem for 6-hr intake.
AMI: amitriptyline, 2.5 mg/kg/day; DMI: desipramine, 2.5 mg/kg/day.

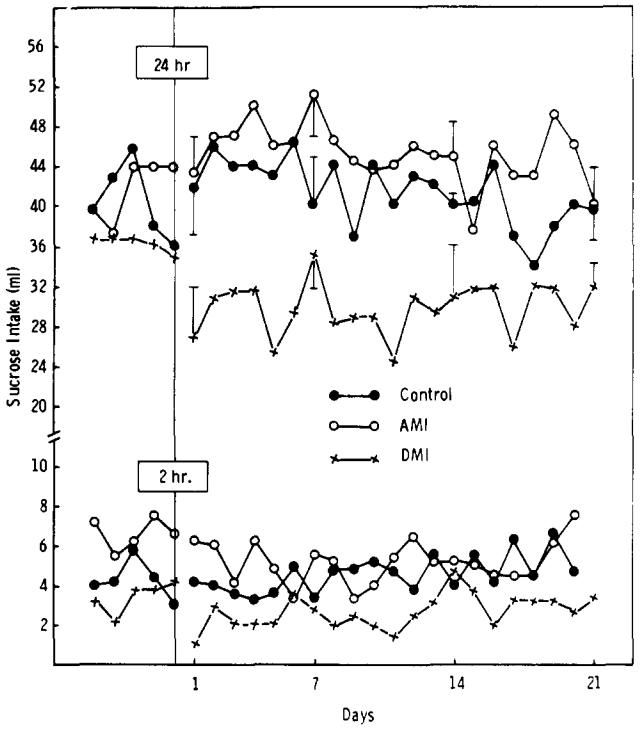

FIG. 6. Sucrose intake for amitriptyline- (AMI, 2.5 mg/kg IP, n=8), desipramine- (DMI, 2.5 mg/kg IP, n=6) or vehicle- (n=5) treated rats in Experiment 4. The vertical line separates baseline from drug administration days. Error bars represent standard errors of the mean.

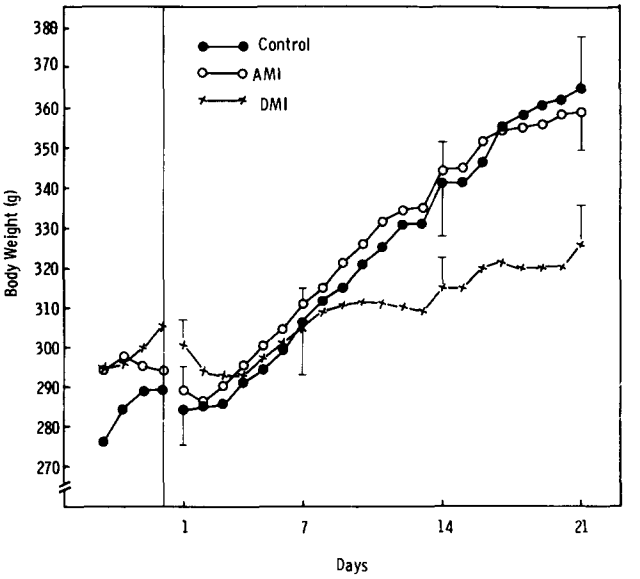

FIG. 7. Body weight data for 21 days of amitriptyline (AMI, 10 mg/kg IP), desipramine (DMI, 10 mg/kg IP) or vehicle in Experiment 5. The vertical line separates baseline from drug administration days. Each point is the mean of 6 male rats, except for DMI, where n=5. Error bars represent standard errors of the mean.

EXPERIMENT 5

Informal observations (S. W. Tang, unpublished) suggested that group housed male rats receiving daily AMI injections might gain weight faster than vehicle-treated rats. Therefore, in this experiment the potential contribution of sex and housing variables was addressed. Male Wistar rats (250–300 g) housed in groups of 6 per cage were used. All animals in a cage received the same drug treatment: 10 mg/kg AMI, 10 mg/kg DMI or saline vehicle. Purina lab chow and water were freely available.

Results

As in the preceding experiments, DMI-treated rats failed to gain weight at the same rates as the other two groups (Fig. 7). A few days after initiation of drug injections, DMI-treated rats were noted to assume a fighting posture soon after the daily injection. After 22 days of drug treatment rats were sacrificed and autopsied. It was found that all DMI-treated rats had clear signs of hemorrhaging in or around the gall bladder. Three of the AMI-treated rats had less severe signs of intraperitoneal hemorrhaging. Gastrointestinal irritation after DMI has been reported previously (e.g., [33]).

EXPERIMENT 6

Assays of final drug level in plasma from animals in the first five experiments consistently revealed measurable

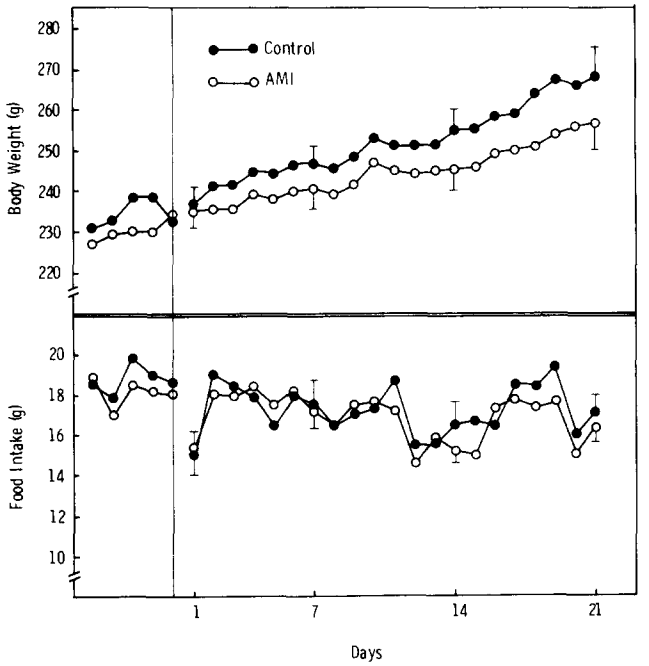

FIG. 8. Body weight and food intake for 21 days of amitriptyline (AMI, n=8) or vehicle (n=5) in Experiment 6. Drug was delivered via Alzet minipumps (see text for average dosage). The vertical line separates baseline from drug administration days. Error bars represent standard errors of the mean.

levels of DMI but only trace amounts of AMI. Specifically, 24 hr after the last daily injection in groups treated with doses of 10 mg/kg, the median concentration of DMI in plasma was 92 ng/ml (range: 60–185 ng/ml), while AMI values were close to zero. Since failure to maintain substantial steady-state plasma levels of AMI could have been a factor in previous results, a technique was sought that would ensure constant plasma levels throughout an experiment. Therefore, in this experiment Alzet osmotic minipumps were used to dispense drug solutions. The pumps (model 2001) released AMI at a rate of 1 μl/hr for 7 days. Pilot trials with DMI solution in these minipumps still resulted in decreased FI and b.wt. gain. For this reason no further tests were performed with DMI.

Individually housed female rats with free access to powdered chow and water were used. This experiment also featured an 18-day pre-drug baseline of daily handling plus FI and b.wt. monitoring before drug treatment began. Pumps were implanted subcutaneously and replaced every 7 days under ether anesthesia. Eight rats received pumps containing AMI solution for a dose of approximately 5 mg/kg/day, and 5 rats received pumps containing 0.85% saline. On the 21st day rats were sacrificed by decapitation and plasma was collected for AMI assays.

Results

Figure 8 shows that AMI-treated rats did not differ from vehicle-treated rats in FI. A slight tendency towards decreased rate of b.wt. gain was found not to be statistically significant. Plasma assays now indicated considerable amounts of AMI in plasma after 21 days (median 42 ng/ml; range: 17–58 ng/ml).

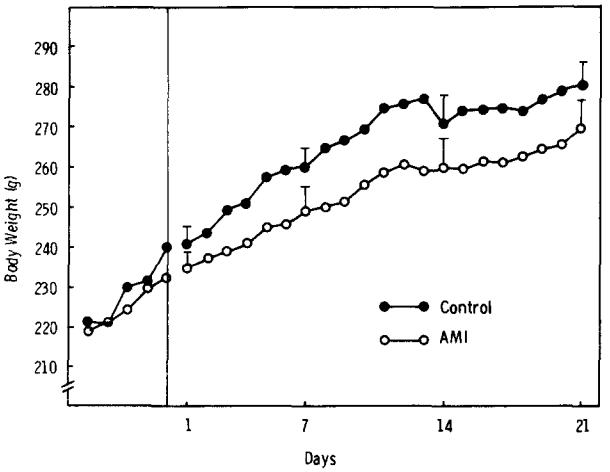

FIG. 9. Body weight for 21 days of amitriptyline (AMI, n=16) and vehicle (n=8) in Experiment 7. Drug was delivered via Alzet minipumps (see text for average dosage). The vertical line separates baseline from drug administration days. Error bars represent standard errors of the mean.

EXPERIMENT 7

A final experiment was conducted using higher doses of AMI (approximately 17 mg/kg/day) continuously delivered through model 2002 Alzet minipumps (0.5 μl/hr for 14 days). In addition, rats were offered a more palatable diet consisting of Borden's sweetened condensed milk (diluted 1:2 v/v with water), a high-fat source (67% Purina powdered chow + 33% Crisco oil w/w), plus regular Purina powdered chow and tap water. One week after the introduction of the palatable diet, 16 rats were implanted with AMI-containing pumps and 8 rats received saline-containing pumps. Pumps were replaced on day 14. Rats were sacrificed on day 28.

Results

Introduction of a palatable diet caused rats to gain weight at a faster rate, as expected. As shown in Fig. 9, AMI-treated rats again showed a tendency towards decreased rate of b.wt. gain. The contribution of each dietary component to total caloric intake remained constant in both groups before and after initiation of drug treatment (data not shown). Plasma assays indicated substantial AMI levels in most rats (mean: 187 ng/ml; range: 32 to 6800 ng/ml). No significant correlations were found between final plasma levels and total weight gain during the experimental period.

DISCUSSION

This series of experiments was performed in an attempt to model in rats the exaggerated weight gain often described by patients undergoing treatment with tricyclic antidepressants. Despite a number of manipulations of dosage, route of administration, diet composition and palatability, chronic TCA treatment was never observed to increase daily food intake or body weight gain. Treatment with DMI consistently led to reduced intake and weight gain, whereas AMI treatment either resulted in no difference from control values or a slight, usually non-significant, tendency towards decreased values. However, chronic treatment with either DMI or AMI

resulted in a significant potentiation of acute caloric intake induced by a systemic injection of 2-deoxy-D-glucose.

Examination of the literature on behavioral effects of other TCAs in rats confirms the tendency observed here towards decreased intake and/or weight gain (e.g., [7,15]). In the specific case of DMI, significant decreases in intake and/or weight gain have been consistently reported (e.g., [36,37]). In addition, Towell *et al.* [35] and Willner *et al.* [37] have reported an enhancement of amphetamine-induced anorexia by DMI. O'Donnell [28] reported decreases in water intake after acute DMI; with repeated DMI treatment, water intake progressively returned to control levels. Blavet and De Feudis [5] reported inhibition of food intake in food-deprived rats by single injections of a number of antidepressants, including DMI and AMI. In fact these authors have suggested that food intake suppression in animals might be useful in screening drugs for antidepressant activity.

Much less attention has apparently been given to investigations of chronic AMI effects on ingestive functions in experimental animals (see [14] for a recent review). In the one systematic work we have been able to locate since conducting our work, Storlien *et al.* [34] found no effect of chronic AMI on food intake or weight gain in rats given access to regular Purina food and/or sucrose solutions.

The present results, consistent with other direct or indirect evidence from the experimental literature, indicate that chronic AMI treatment does not by itself result in increased appetite and/or b.wt. gain in normal rats. While not every patient on AMI gains weight [4], examination of individual data indicated that not a single animal in these experiments showed exaggerated weight gain. To the extent that normal rats can be used to probe non-psychiatric components of clinically active compounds, these findings appear incongruous with the many reports that AMI increases appetite and/or weight gain in patients independent of its mood altering effects (e.g., [3, 18, 29, 31]). At least three possibilities might be suggested to account for this discrepancy. First, there may be some fundamental difference between the general pharmacology of AMI in humans and rodents. In this case one might expect chronic AMI to produce significant changes in appetite/b.wt. in normal human volunteers and also possibly in non-human primates, but not necessarily in rats or mice. We are unaware of any existing data which provide evidence for or against this possibility. Second, it is possible that the FI/b.wt. effects of AMI on humans result from some interaction between the effects of the drug and specific physiologic alterations associated with depressive illness, possibly, but not necessarily, the psychiatric symptoms presented by the patients. Recently Fernstrom [13] reported significant reductions in resting metabolic rate in patients treated with AMI or imipramine and suggested that this might be a factor in increased weight gain. It would be of interest to test whether AMI is capable of inducing such decreases in basal metabolic rate in normal volunteers and in experimental animals or whether this results from an interaction with physiologic conditions characteristic of affective illness. Finally, it is possible that FI/b.wt. changes observed in humans do not reflect a direct effect on internal physiological controls over "hunger." Instead, it is possible that chronic AMI somehow augments reactivity to external cues for the initiation of feeding. In other words, AMI treatment might not elicit chronic hunger and/or decreased metabolic activity, but might instead sensitize the organism towards acute stimuli capable of eliciting food intake. This possibility is supported by our finding of increased caloric intake in response to 2-DG after chronic AMI or DMI (Experiment 4). 2-Deoxy-D-glucose in large systemic doses as used here is known to cause sympatho-medullary and pituitary-adrenal discharge [17] and other signs usually associated with stress reactions [6]. Along this line, Rowland [32] has suggested that the feeding response to 2-DG may also be stress-related. Other evidence from this laboratory indicates that AMI-treated rats, while failing to show daily increases in FI/b.wt. under normal conditions, overeat in response to arousing tail-pinch stimulation [26]. We have also found that AMI-treated rats show potentiated feeding responses to intrahypothalamic injections of NE [27], a procedure that is also associated with increased activity in the hypothalamic-pituitary-adrenal axis [22]. If the latter notion of increased susceptibility to arousing/stressful stimuli is correct, one would expect the weight gain problems of AMI-treated patients to be at least in part related to a predisposition to overeat in response to stress or other external arousing stimuli.

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